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Supramolecular organization of bacterial aerobic respiratory chains: From cells and back☆

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ABSTRACT

Aerobic respiratory chains from all life kingdoms are composed by several complexes that have been deeply characterized in their isolated form. These membranous complexes link the oxidation of reducing substrates to the reduction of molecular oxygen, in a process that conserves energy by ion translocation between both sides of the mitochondrial or prokaryotic cytoplasmatic membranes. In recent years there has been increasing evidence that those complexes are organized as supramolecular structures, the so-called supercomplexes and respirasomes, being available for eukaryotes strong data namely obtained by electron microscopy and single particle analysis. A parallel study has been developed for prokaryotes, based on blue native gels and mass spectrometry analysis, showing that in these more simple unicellular organisms such supercomplexes also exist, involving not only typical aerobic-respiration associated complexes, but also anaerobic-linked enzymes. After a short overview of the data on eukaryotic supercomplexes, we will analyse comprehensively the different types of prokaryotic aerobic respiratory supercomplexes that have been thus far suggested, in both bacteria and archaea. This article is part of a Special Issue entitled Organization and dynamics of bioenergetic systems in bacteria, edited by Prof Conrad Mullineaux.

1. Brief overview of aerobic respiratory chains investigation

The aerobic respiratory chain is one of the most relevant pathways in cells, for it makes possible the occurrence of other pathways dependent on energy supply. ATP molecules are the energy currency in the living world, and the most effective one, for the amount of energy conserved in its phosphate bond is just enough to empower enzymatic reactions, contributing to an efficient use of energy by the cell. Other very energetic molecules in the cell, for example NADH and glucose, contain much more energy, and if used would constitute not only a waste, but also its dissipation as heat could seriously jeopardize cells.

Driven by this fact, and also by curiosity, research over the respiratory pathway gained emphasis by the second half of the 20th century and never stopped to increase in relevance in understanding the basics of life, but also to explain health and disease, youth and aging. Besides the genius and persistence of researchers, the progresses in this field have been boosted and brake by advances in technology.

A brief chronology of a few major steps further into the knowledge of respiratory chains are listed:

1) The spectrophotometric characterization of mitochondria [1] and oxidative phosphorylation states [2] by Chance and Williams, benefiting from the development of the spectrophotometer by Arnold Beckman in 1940 and the Clark oxygen electrode in the fifties; 2) The chemiosmotic [3] and conformational [4] theories of Peter Mitchel and Paul Boyer, respectively, in the late sixties; 3) The 3-D structure of ATP synthase [5], by John Walker, in the nineties, as well as of the other respiratory complexes; 4) The development of the Blue Native Polyacrylamide Gels BN-PAGE technique and its application to the characterization of mitochondrial complexes that led to the identification of respiratory supramolecular structures [6], by Herman Schagger also in the nineties; Improvements in mass spectrometry analysis enabled sequencing of the less abundant and more difficult to ionize membrane proteins, namely liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), allowing to detail the composition of the complexes visualized in the BN-PAGE; 5) The generation of 3D models from the analyses of such supramolecular structures, by means of electron microscopy and single particle analysis, particularly boosted by Boekema's group already in the 21st century [7]; and finally, 6) The development of electron tomography and its application to mitochondria, to which Terry Frey [8] and Werner Kuhlbrandt [9] greatly contributed. Throughout this evolution, a movement in the object of the study from

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cells to organelles, to isolated complexes, and back to supramolecular structures, organelles and cells is observed, reflecting the actual need to integrate the innumerous contributions into a global perspective of the oxidative phosphorylation pathway and of this into the cell.

2. Oxidative phosphorylation

In both eukaryotic and prokaryotic aerobic worlds, there is a process by which the reducing equivalents, resulting from cell sugar, lipid and amino acid catabolism, are oxidized via a chain of enzymes, the respiratory chain, that culminate in the reduction of oxygen to water. Throughout this chain, some redox reactions are coupled to ion-translocation across the membrane, forming a transmembrane ion-motive force that is used by ATP synthase to synthesize ATP. This process is the so-called oxidative phosphorylation.

2.1. Mammalian mitochondria respiratory chain

In detail, and in mammalian mitochondria, the so-called paradigm, the oxidative phosphorylation (OXPHOS) pathway is mainly composed by the NADH:ubiquinone oxidoreductase or complex I, the succinate:ubiquinone oxidoreductase (SQR) or complex II, the bc_1 ubiquinol:cytochrome *c* oxidoreductase or complex III, the aa_3 cytochrome *c*:oxygen oxidoreductase or complex IV, and the ATP synthase also known as complex V (Fig. 1). The flow of electrons between complexes I or II and complex III is mediated by the lipophilic molecule, ubiquinone, and from complex III to complex IV, the electrons pass by the soluble electron carrier cytochrome *c*, located in the intermembrane space. Proton translocation occurs from the matrix to intermembrane space by complexes I, III and IV, conserving energy in a proton motive force that is used in the synthesis of ATP [10], or in motility and ion transport.

2.2. Diverging from the model

Protists, fungi and plant mitochondria have additional enzymes, namely alternative rotenone-insensitive NAD(P)H:quinone oxidoreductases, or type II NAD(P)H dehydrogenases (e.g. [11,12,13]), some of which are sensitive to calcium (e.g. [14]), and alternative oxidases (AOX) (e.g. *Arum maculatum* [15]).

2.3. OXPHOS organization

Three models try to account for the organization of the OXPHOS pathway in the inner membranes of mitochondria or the plasma membranes of prokaryotes. The solid state model based on the knowledge that the transfer of electrons from reducing substrates to oxygen occurred via a sequentially organized cytochrome pathway, that included cytochromes *b*, *c*, *a* and a_3, proposes that these enzymes would be tightly packed in a spatial arrangement ensuring substrate accessibility and a high catalytic rate [16]. The random collision model suggested by Hackenbrock and co-workers, aware of the possibility to purify and reconstitute functionally active respiratory chain complexes, postulated the need of multiple collisions to accomplish electron transfer within the respiratory components [17]. In this model, the respiratory enzymes diffuse laterally and independently of each other, occurring multicollisional electron transfer, dependent on the redox components diffusion rate [18]. The more recent plasticity model tries to reconcile the solid state and the random collision models. It suggests a dynamic model where individual complexes and supramolecular organizations comprising sets of different individual complexes coexist, assembling and disassembling on cell demand (e.g. [19]).

2.4. Supramolecular organization of OXPHOS—respiratory supercomplexes

Although supramolecular assemblies of respiratory chain enzymes have been identified in all domains of life, based on evidences from multiple technical approaches (see below), the existence of supercomplexes is still a matter of debate, particularly in the prokaryotic world. For instance, kinetic data in yeast mitochondria showed that cytochrome *c* may be pre-bound to the aa_3 oxygen reductase, but this interaction is determined by the bimolecular interactions between these two proteins and their stoichiometric ratio, rather than by an effective trapping of the soluble carrier within a particular supramolecular structure [20]. This implies that the behavior of this respiratory chain segment is in agreement with the random collision model [[17]].

In fact, supercomplexes have been proposed as a strategy to a better efficiency of the respiratory pathway, not only allowing higher yields of energy conservation, by enabling substrate channeling [21] and enhancing the stability of the respiratory enzymes [22], but also, and due to the former, by minimizing the production of reactive oxygen species [23].

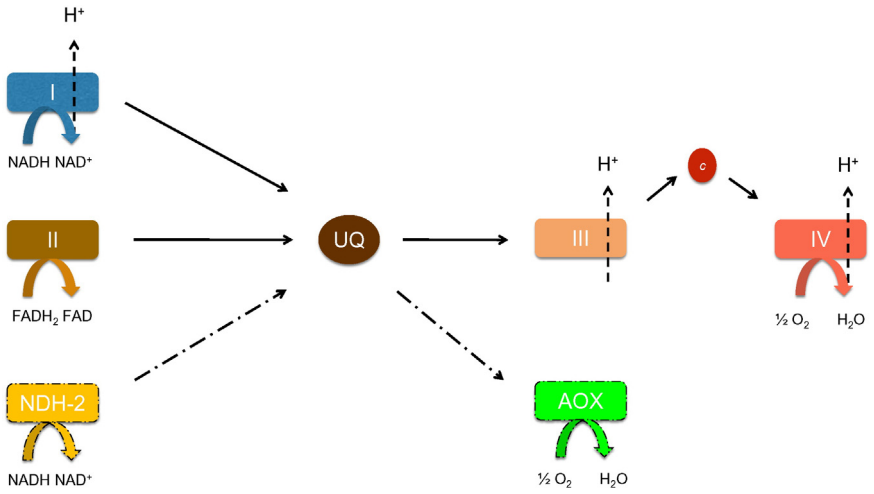

Fig. 1. Mammalian mitochondria electron transfer chain. In dashed boxes the alternative enzymes present in the mitochondria of plants and fungi. I, II, III and IV, NADH:ubiquinone oxidoreductase (complex I), succinate:ubiquinone oxidoreductase (complex II), ubiquinol:cytochrome c oxidoreductase (complex III) and cytochrome c:oxygen oxidoreductase (complex IV), respectively. NDH-2, type II or alternative NADH dehydrogenase, AOX, alternative oxidase. Solid arrows represent the direction of electron flow; dashed arrows for alternative pathways.

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